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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 203/04, 203/06
C07D 493/04, A61K 31/60
A61K 31/62, 31/625 //
(A61K 31/60, 31:21)
(A61K 31/60, 31:34)

A3

(11) International Publication Number: WO 94/03421

(43) International Publication Date: 17 February 1994 (17.02.94)

(21) International Application Number: PCT/IE93/00040

(22) International Filing Date: 26 July 1993 (26.07.93)

(30) Priority data:
922474 30 July 1992 (30.07.92) IE

(71) Applicant *(for all designated States except US)*: CAL INTERNATIONAL LIMITED [IE/IE]; 15 Butterfield Park, Rathfarnham, Dublin 14 (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BYRNE, William [IE/IE]; 6 Mather Road North, Mount Merrion, County Dublin (IE). RYNNE, Andrew [IE/IE]; 2 Liffey Lawns, Clane, County Kildare (IE).

(74) Agents: O'CONNOR, Donal, H. et al.; Cruickshank & Co., 1 Holles Street, Dublin 2 (IE).

(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DE (Utility model), DK, DK (Utility model), ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
31 March 1994 (31.03.94)

(54) Title: ESTERS AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

(57) Abstract

A pharmaceutical product for relief of the symptoms of angina pectoris and the like comprises an ester or a combination of an organic nitrate, and a salicylate, or derivative thereof, having anti-platelet activity.

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/IE 93/00040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C203/04 C07C203/06 C07D493/04 A61K31/60 A61K31/62
A61K31/625 //(A61K31/60,31:21),(A61K31/60,31:34)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

	Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
3	X	WO,A,92 01668 (ITALFARMACO S.P.A.) 6 February 1992 see page 8, line 7-24 see page 11, line 3-14; claims; examples 8,11	1-4, 13-17,33
3	P,X	WO,A,92 16506 (ITALFARMACO, S.P.A.) 1 October 1992 see page 2, line 10-23; claims; example 8	1-4, 13-17,33
2	X,Y	EUR. HEART J. vol. 12 SUP.A , 1991 pages 2 - 4 C.R. CONTI 'Why use a nitrate in 1990?' see the whole document	1-47

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

5

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 1994	15.02.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Orviz Diaz, P

Form PCT/ISA/210 (second sheet) (July 1992)

Int. ional Application No
PCT/IE 93/00040

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT.

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EUR. HEART J. vol. 9 SUP. A , 1988 pages 45 - 49 R. DE CATERINA 'Mechanisms for the in vivo antiplatelet effects of isosorbide dinitrate.' see the whole document	1-47
X,Y	EUR. J. CLIN. PHARMACOL. vol. 25 , 1983 pages 779 - 782 E. REY 'Pharmacological interaction between nitroglycerin and aspirin after acute and chronic aspirin treatment of healthy subjects.' see the whole document	1-47
X,Y	J. CARDIOVASC. PHARMACOL. vol. 5, no. 5 , 1983 pages 874 - 877 S. WEBER 'Influence of aspirin on the hemodynamic effects of sublingual nitroglycerin.' see the whole document	1-47
Y	EP,A,0 449 426 (INTERNATIONAL MEDICAL RESEARCH LIMITED) 2 October 1991 see the whole document	1,3-12, 14-17, 33-47

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 93/00040

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

FOR FURTHER INFORMATION PLEASE SEE FORM PCT/ISA/206 SENT 13/12/93

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/IE 93/00040

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9201668	06-02-92	AU-A-	8097491	18-02-92
		EP-A-	0540544	12-05-93
WO-A-9216506	01-10-92	AU-A-	1347992	21-10-92
		EP-A-	0576475	05-01-94
EP-A-0449426	02-10-91	US-A-	5156849	20-10-92

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C07D 493/04, A61K 31/62
A61K 31/625, 31/60 // (A61K 31/60
A61K 31:21) (A61K 31/60
A61K 31:34)

A2

(11) International Publication Number: WO 94/03421

(43) International Publication Date: 17 February 1994 (17.02.94)

(21) International Application Number: PCT/IE93/00040

(22) International Filing Date: 26 July 1993 (26.07.93)

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Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ESTER AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

(57) Abstract

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ESTER AND COMBINATIONS OF AN ORGANIC NITRATE AND A SALICYLATE

The invention relates to pharmaceutical products.

The term "organic nitrates" as used in this specification refers to pharmacologically active organic nitrate compounds which relieve, or act as prophylactic against, angina pectoris.

Organic nitrates are dilators of arterial and venous smooth muscle. The dilation action on the venous system increases the venous capacity allowing pooling of venous blood. This in turn reduces the volume of blood returning to the heart thereby lessening the strains on the heart muscle by reducing the pressure in the heart chambers (ventricles). This, in turn, reduces the oxygen requirements of the heart muscle. The dilation action on the arterial system is achieved by increasing the volume of the arterial system with consequent lower resistance to blood flow. This, in turn, reduces the work that the heart is required to do. In the coronary arteries (heart) a transient widening of the arteries (vasodilation) increases blood circulation to the heart muscle thereby increasing oxygen availability to the heart muscle.

Patients with coronary artery narrowing may suffer from angina pectoris which is usually brought on by exercise, motion or eating. The organic nitrates by virtue of their action described above relieve the symptoms of angina pectoris.

In more detail, organic nitrates act in two ways - indirectly and directly.

Indirectly: they are smooth muscle relaxants and thus dilate both arterial and venous blood vessels. At lower

doses their action is mainly on the venous system resulting in a decreased right and left ventricular filling pressure. At lower doses, however, they have little effect on the systemic (arterial) filling pressure. At higher doses, the arterial effects are more marked and decreased systemic resistance is accompanied by a reduction in blood pressure (Flaherty et al 1976). The venodilating and arterial effects of nitrates relieve ischaemia (the cause of angina, pain) by reducing determinates of myocardial oxygen demand.

Directly: they relieve ischaemia by direct action on the coronary vasculature thereby increasing intercoronary collateral flow and reversal of coronary artery spasm.

One widely used organic nitrate is isosorbide mononitrate (ISMN) which is an active metabolite of Isosorbide dinitrate (ISDN). ISMN has a high bioavailability and has a comparatively long half life (4-5 hours). Thus it is very suitable for prophylactic angina therapy. This is particularly so when it is presented as a sustained release formulation.

According to the invention there is provided a pharmaceutical product comprising:

an organic nitrate; and

a salicylate or a salt, ester, derivative, complex thereof, or salts of the ester, derivative or complex having anti-platelet activity.

In a particularly preferred embodiment of the invention, the pharmaceutical product is a salicylate ester of an esterifiable organic nitrate.

Preferably, the organic nitrate is directly esterifiable. In other words, the organic nitrate has an hydroxy group which is available for esterification.

The organic nitrate may be an isosorbide nitrate such as isosorbide 2-mononitrate or, most preferably isosorbide 5-mononitrate.

Alternatively, the organic nitrate is a glyceryl nitrate such as glyceryl trinitrate (also known as 1,2,3-Propanetriol trinitrate and Nitroglycerin).

Alternatively, the organic nitrate is a pentaerythritol nitrate such as pentaerythritol trinitrate (also known as Pentrinitrol).

Alternatively, the organic nitrate may be indirectly esterifiable by removal of a nitrate from the nitrate compound and replacement by an hydroxy group prior to esterification.

In this case, the organic nitrate may be selected from the group consisting of Erythritol Anhydride, Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propatyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

In a particularly preferred embodiment of the invention the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

The product may be adapted for oral administration or percutaneous administration.

The invention also provides a tablet or capsule comprising a pharmaceutical product of the invention.

The invention further provides a transdermal patch including a pharmaceutical product of the invention.

The invention especially preferably provides the compound Isosorbide 5-mononitrate-2-aspirinate.

In another aspect the invention provides a process for preparing a pharmaceutical product of the invention which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

Preferably, the esterification is carried out using a coupling reagent and/or a catalyst.

The coupling agent typically is a carbodiimide such as Dicyclohexylcarbodiimide (DCC).

The catalyst may comprise a pyridine derivative or paratoluene sulphonic acid.

Preferably, the esterification is carried out in non-aqueous conditions.

Typically, the process is carried out using methylenechloride as a solvent.

Preferably the process is carried out at a temperature below 5°C, most preferably at 0°C or below.

In another aspect of the invention the product is a combination product of the organic nitrate and the anti-platelet agent.

Preferably, the anti-platelet agent comprises acetylsalicylic acid.

In a preferred arrangement, the weight ratio of organic nitrate to acetylsalicylic acid is from 2:1 to 1:5, most preferably approximately 1:1.

The component products may be separated from each other in a single dose form. The barrier may be a physical barrier such as a membrane between the components. The membrane may be a coating of the components in microgranular or granular presentation. The coating may be on any or all of the components within the formulation.

Alternatively, the barrier is a chemical barrier.

Preferably, at least a portion of the organic nitrate is present in a slow release form.

Most preferably, the combination product comprises a capsule including the components.

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE 1

Synthesis of acetylsalicyloxyisosorbide mononitrate

Materials:

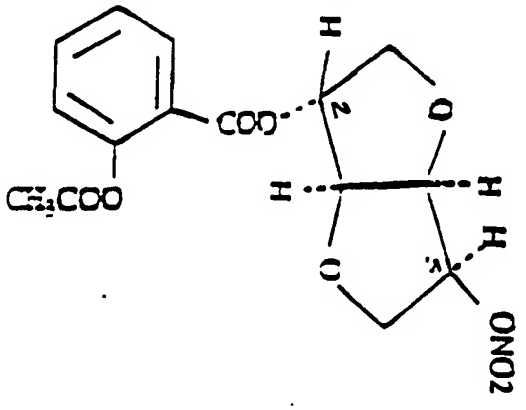
Acetylsalicylic acid
Isosorbide mononitrate
Dicyclohexylurea (DCC)
Dimethylaminopyridine (DMAP)

Dichloromethane (dry)
Citric acid solution (20%w/v in water)
Sodium bicarbonate aqueous solution saturated
Sodium sulphate anhydrous

Method:

Add DMAP (0.03 gm) and isosorbide mononitrate (1.85gm,0.01M) to a cold (0°C) and well stirred solution of acetylsalicylic acid (1.8gm, 0.01M) in dry dichloromethane (10ml). Gradually add DCC (2.06gm,0.01M). Stir for 10 minutes before removing the icebath and then stir for 3 hours at room temperature. Remove the precipitate by filtration. The filtered solution was washed with 2 x 25ml aliquots of cold 20% citric acid solution and then 2 x 25ml aliquots of saturated sodium bicarbonate solution. Dry the lower organic layer with anhydrous sodium sulphate filter and remove the solvent in vacuo. The product is purified on a sigel column using dichloromethane as eluent. The yield of the oily semisolid product was 50-75%.

The product has the following structure:



The product may be named as Isosorbide-5-mononitrate-2-aspirinate, or 2-{2-Acetoxybenzoyl}-isosorbid -5-

mononitrate, or 2-Acetylsalicyloxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate.

Oil/low melting point solid Molecular formula $C_{15}H_{15}O_9N$
Molecular weight 353

Infra red spectrum (thin film) 1780,1740,1640 cm-1 The infra red analysis for isosorbide mononitrate is shown in Fig. 1. Fig. 2 is the infra red analysis for the product of the example.

Proton magnetic Resonance Spectrum See PMR BB-24 appended

Thin Layer Chromatogram: Sigel GF 254/dichloromethane rf=0.8

Mass spectrum (EI) MI 353

Because of the inherent lability of the starter and product ester groupings it is necessary to select mild reaction conditions. The general method of Neises, B and Steglich, W, Angew. Chem. Int Ed Eng. 17 (1978) No. 7, 522-524 was selected because of the mild reaction condition. The direct formation of acetylsalicyloxyisosorbide-5-mononitrate from acetylsalicylic acid and isosorbide - 5-mononitrate is accomplished by the use of the coupling reagent N,N1-dicyclohexylcarbodiimide (DCC). The particular virtue of this method lies in its suitability for acid sensitive substrates such as esters. The rate of reaction is greatly increased by addition of catalytic amounts of 4-dimethylaminopyridine. Pyridine or p-toluene sulphonic acid may also be used.

Indirect Esterification

Acid chlorides react with primary and secondary alcohols to give esters in good yield.

Anhydrides may also be used for the esterification of alcohols in the presence of a suitable catalyst. Acidic catalysts such as sulphuric acid or zinc chloride and basic catalysts such as pyridine are generally used.

Direct Esterification

Direct esterification procedures involving carboxylic acids and alcohols can be accomplished by the addition of concentrated sulphuric acid or dry HCl to the reaction mixture.

Various methods for the preparation of esters are described in "Comprehensive Organic Transformations" - A guide to functional group preparations by Richard C. Larock, VCH Publishers Inc 1989, especially pages 966-972, 978-979, 980-981, 985-987, 989-990.

As the product of Example 1 is an oil/low melting point solid, it is likely to be particularly suitable for percutaneous application, by means of a transdermal patch or for oral application in the form of a capsule, such as a soft gelatin capsule.

A widely used organic nitrate is Isosorbide Mono or di nitrate. Such agents act directly on the coronary arteries dilating them and thus improving the blood flow to the heart muscle and thus relieving the pain of angina pectoris. Another way that organic nitrates in general relieve the pain of angina is by reducing the requirements of the myocardium (heart muscle) for oxygen by reducing the volume of blood returning to the heart.

The pharmaceutical products of the invention are particularly for the prophylaxis of chronic stable angina pectoris. The invention provides a new combined prophylactic therapy which will deal with the pain of angina and decrease the risk of thrombosis leading to heart attack. Patients with angina pectoris have diseased coronary arteries. All patients with this degree of diseased coronary arteries are at increased risk of developing thrombosis (or clot).

In a particularly preferred embodiment of the invention the anti-platelet agent is ASPIRIN (acetylsalicylic acid).

Aspirin has been widely used for many years as an analgesic/anti-pyretic and anti-inflammatory agent. As such, it is a most useful drug. In more recent years, however, it has been discovered that aspirin has a powerful anti-platelet effect. Platelets are microscopic particles within the blood that, under certain circumstances, can stick together to form a thrombus (clot). Aspirin prevents the sticking together of platelets and thus helps prevent the occurrence of heart attack or its complications.

In the case of a two component product preferably the composition is in a form suitable for oral administration, typically in a tablet or capsule form.

The weight ratio of the nitrate to Aspirin may be from 2:1 to 1:5, most preferably 1:1.

In the case of a two component product the component products may be separated from one another in a single dose form. They may be separated by a barrier such as a

physical barrier provided between the components in a single capsule.

The component products may be separated from each other by a coating of gelatine or the like on one of the components, most preferably on the nitrate.

Alternatively, the barrier may be a chemical barrier, each of the components being present in a microgranulated form.

The composition may be arranged for any desired release profile. The components may be released simultaneously or in some cases the organic nitrate is released more slowly than the Aspirin.

The effect of the pharmaceutical product of the invention is in the treatment of angina pectoris and in reducing the risk of developing myocardial infarction.

It is anticipated that, while the invention has been specifically described with reference to the combination of Isosorbide nitrate and Aspirin, it is expected that combination products of other known anti-angina agents are anti-platelet agents may also be used in combination.

Providing a nitrate and an anti platelet agent in a single dose pharmaceutical product has considerable advantages from a compliance viewpoint. If a patient is required to take a nitrate and aspirin separately there is a risk that one or other will be forgotten. It is also quicker and easier for a doctor to prescribe such a combination product.

EXAMPLE 2

A capsule containing 8 mg of Aspirin, 15 mg of Isosorbide Mononitrate for immediate release and a slow release tablet containing 45 mg of Isosorbide Mononitrate.

A size 1 capsule was used. The ideal powder fill weight was in the region of 190 mg, containing 80 mg and 15 mg of Isosorbide Mononitrate respectively. The formulation for the powder fill was:

A.	Aspirin	80 mg
	ISMN	15 mg
	Microcrystallinecellulose	90 mg
	Talc	4 mg
	Magnesium Stearate	1 mg

A number of alternative formulations for a slow release tablet containing 45 mg of Isosorbide Mononitrate were made. The preferred formulation was:

B.	ISMN	45.0 mg
	Calcium H. Phosphate	30.0 mg
	Eudragit NE 40D	15.0 mg
	Magnesium Stearate	1.0 mg
	Water	q/s

The ISMN was blended with Calcium H. Phosphate and the resultant mix was granulated with Eudragit. The granules were sieved using a No. 10 sieve and dried at 40°C for 6 to 8 hours. Magnesium stearate and talc were added and the mixture was blended prior to compression.

Dissolution tests of the capsule incorporating A and B yielded a good longterm release profile which is plotted in Fig. 3.

EXAMPLE 3

Example 2 was repeated except that the granules of Example 2B were further blended with Eudragit RS/PO.

The results of dissolution tests are plotted in Fig. 4.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A pharmaceutical product comprising:

an organic nitrate; and

a salicylate or a salt, ester, derivative, complex thereof, or salts of the ester, derivative or complex having anti-platelet activity.

2. A pharmaceutical product as claimed in claim 1 wherein the pharmaceutical product is a salicylate of an esterifiable organic nitrate.

3. A pharmaceutical product as claimed in claim 1 or 2 wherein the organic nitrate is indirectly esterifiable.

4. A pharmaceutical product as claimed in claim 1 or 2 wherein the organic nitrate is directly esterifiable.

5. A pharmaceutical product as claimed in claim 4 wherein the organic nitrate is an isosorbide nitrate.

6. A pharmaceutical product as claimed in claim 5 wherein the organic nitrate is isosorbide 5-mononitrate.

7. A pharmaceutical product as claimed in claim 5 wherein the organic nitrate is isosorbide 2-mononitrate.

8. A pharmaceutical product as claimed in claim 4 wherein the organic nitrate is a glyceryl nitrate.

9. A pharmaceutical product as claimed in claim 8 wherein the glyceryl nitrate is glyceryl trinitrate (1,2,3-Propanetriol trinitrate) (Nitroglycerin).

10. A pharmaceutical product as claimed in claim 4 wherein the organic nitrate is a pentaerythritol nitrate.

11. A pharmaceutical product as claimed in claim 10 wherein the pentaerythritol nitrate is pentaerythritol trinitrate (Pentrinitrol).

12. A pharmaceutical product as claimed in claim 3 wherein the organic nitrate is selected from the group consisting of Erythritol Anhydride, Mannitol Hexanitrate, Trolnitrate Phosphate, Pentaerythritol Tetranitrate, Propatyl Nitrate, Clonitrate, and Isosorbide Dinitrate.

13. A pharmaceutical product as claimed in any of claims 2 to 12 wherein the product is formed by esterification of an esterifiable organic nitrate with acetylsalicylic acid.

14. A pharmaceutical product as claimed in any preceding claim which is adapted for oral administration.

15. A pharmaceutical product as claimed in any of claims 1 to 13 which is adapted for percutaneous administration.

16. A tablet or capsule comprising a pharmaceutical product as claimed in any of claims 1 to 14.

17. A transdermal patch including a pharmaceutical product as claimed in any of claims 1 to 13 or 15.

18. Isosorbide 5-mononitrate-2-aspirinate.

19. A transdermal patch including isosorbide 5-mononitrate-2-aspirinate.

20. A soft capsule including isosorbide 5-mononitrate-2-aspirinate.

21. A process for preparing a pharmaceutical product as claimed in any of claims 2 to 20 which comprises esterifying an esterifiable organic nitrate with acetylsalicylic acid.

22. A process as claimed in claim 21 wherein the esterification is carried out using a coupling reagent.

23. A process as claimed in claim 21 or 22 wherein the esterification is carried out using a catalyst.

24. A process as claimed in claim 22 or 23 wherein the coupling agent is a carbodiimide.

25. A process as claimed in claims 23 or 24 wherein the catalyst is a pyridine derivative.

26. A process as claimed in claims 23 or 24 wherein the catalyst comprises paratoluene sulfonic acid.

27. A process as claimed in any of claims 21 to 26 wherein the esterification is carried out in non-aqueous conditions.

28. A process as claimed in claim 27 wherein the process is carried out using methylenechloride as a solvent.

29. A process as claimed in any of claims 21 to 28 wherein the process is carried out at a temperature below 5°C.

30. A process as claimed in any of claims 21 to 28 wherein the process is carried out at a temperature of 0°C or below.

31. A process substantially as hereinbefore described with reference to the Examples.

32. A pharmaceutical product whenever prepared by a process as claimed in any of claims 21 to 31.

33. A pharmaceutical product substantially as hereinbefore described with reference to the Examples.

34. A product as claimed in any of claims 1, 2 to 12, or 14 to 17 which is a combination product of the organic nitrate and the anti-platelet agent.

35. A product as claimed in claim 34 wherein the anti-platelet agent comprises acetylsalicylic acid.

36. A composition as claimed in claim 35 wherein the weight ratio of organic nitrate to acetylsalicylic acid is from 2:1 to 1:5.

37. A composition as claimed in claim 36 wherein the weight ratio is approximately 1:1.

38. A composition as claimed in claim 34 to claim 37 wh rein the component products are separated from each other in a single dose form.

39. A composition as claimed in claim 38 wherein the component products are separated from each other by a barrier.

40. A composition as claimed in claim 38 wherein the barrier is a physical barrier.

41. A composition as claimed in claim 40 wherein the physical barrier is a membrane provided between the component products.

42. A composition as claimed in claim 41 wherein the membrane is a coating of the components in microgranular or granular presentation.

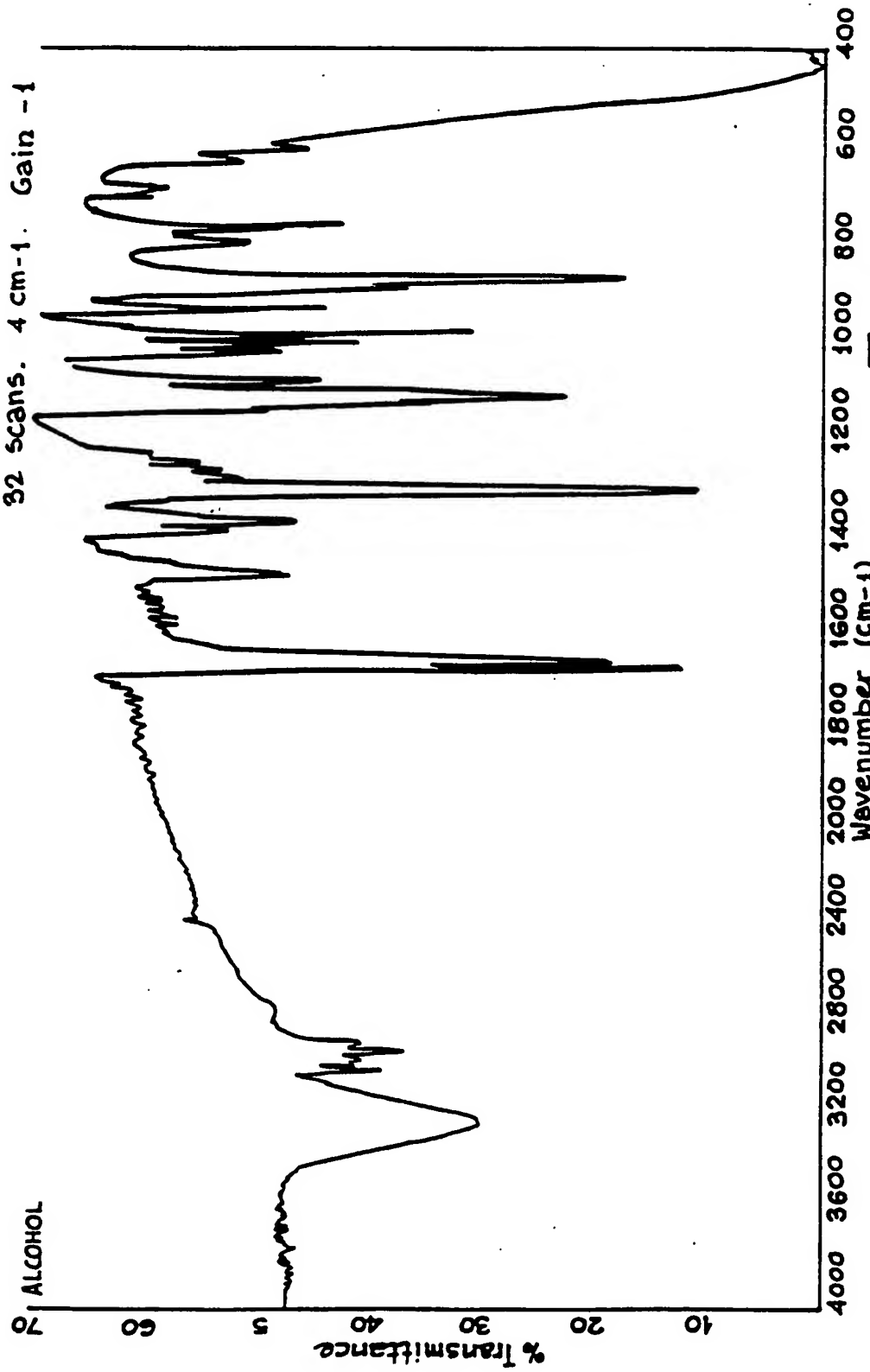
43. A composition as claimed in claim 42 wherein the coating is provided on any one or all of the components within the formulation.

44. A composition as claimed in claim 38 wherein the barrier is a chemical barrier.

45. A product as claimed in any of claims 34 to 44 wherein at least a portion of the organic nitrate is present in a slow release form.

46. A product as claimed in any of claims 34 to 45 wherein the combination product comprises a capsule including the components.

47. A combination pharmaceutical product as claimed in any of claims 34 to 46 substantially as hereinbefore described with reference to the Examples.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% Transmittance
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60
5
40
30
20
10
Wavenumber (cm-1)
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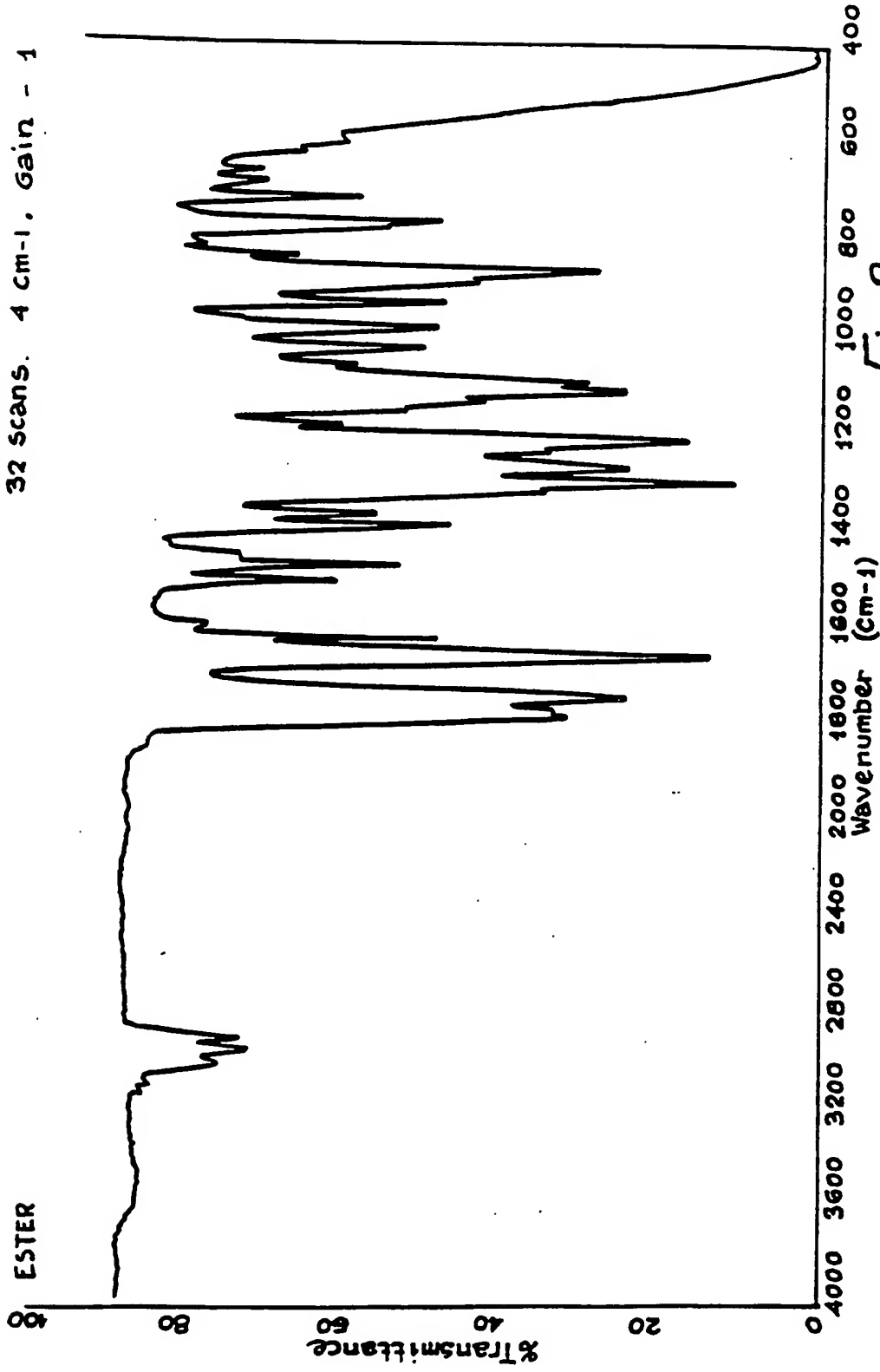
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400

Fig.1


32 scans. 4 cm-1. Gain - 1
ESTER
% Transmittance
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20
40
60
80
100
4000
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1200
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800
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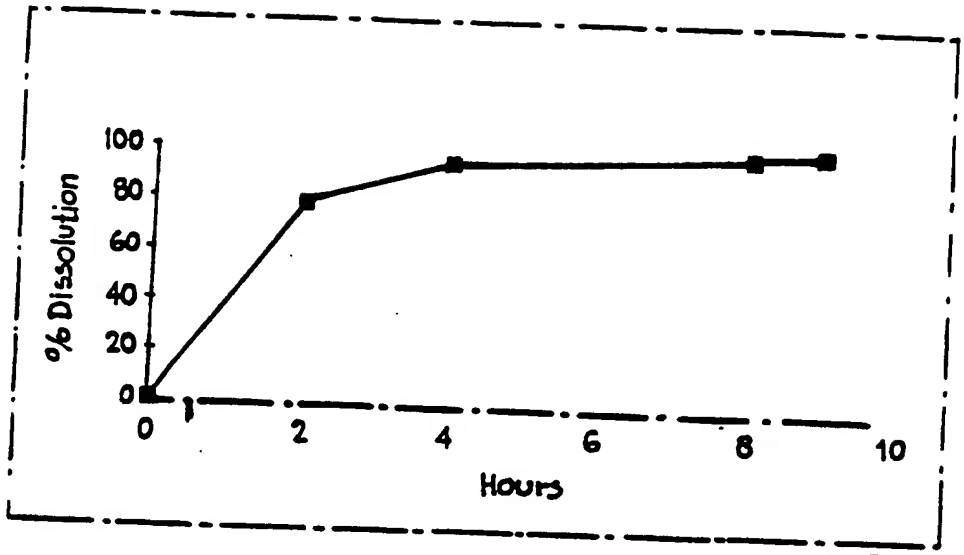
400
Wavenumber (Cm-1)

Fig. 2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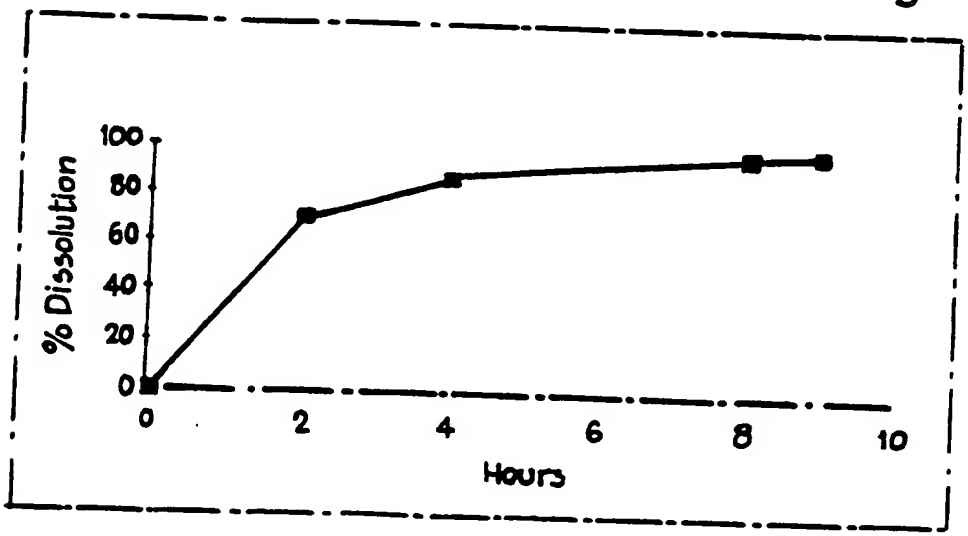
60
40
20
0
0
2
4
6
8
10
Hours

Fig.3


% Dissolution
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2
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6
8
10
Hours

Fig.4